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A RETROSPECTIVE ANALYSIS OF THE CLINICAL RESULTS IN RELATION TO THE RAPPAPORT HISTOLOGICAL CLASSIFICATION

T. C. BROWN, M. V. PETERS, D. E. BERGSAGEL AND J. REID

From the Princess Margaret Hospital, Toronto, Canada

Summary.—The Rappaport classification of the non-Hodgkin's lymphomata was applied to 460 cases at the Princess Margaret Hospital. Statistically significant differences in the numerical incidence between the nodular and diffuse patterns was found for the entire series and for the lymphocytic, " histiocytic " and mixed cell types individually. All of the undifferentiated types were diffuse. These differences were sustained for the degrees of differentiation within the lymphocytic group. The " histiocytic " group was not subclassified by differentiation. The cell types differed in the numerical distribution of the patterns. The lymphocytics were predominantly diffuse but their nodular forms constituted a higher proportion of the nodular pattern than did their diffuse types of the diffuse group. More of the well differentiated lymphocytics were nodular than were diffuse and they formed a higher proportion of the nodular group than they did of the diffuse. On the other hand, the poorly differentiated lymphocytics were predominantly diffuse and these were less well represented in the nodular group than in the diffuse tumours. The intermediate differentiated types were usually diffuse but slight better represented in the nodular group. Most tumours of the " histiocytic " type were diffuse and these constituted a higher proportion of diffuse than the nodular tumours. The mixed cell lesions were predominantly nodular and comprised a much higher proportion of nodular lesions than diffuse.

No real differences were identified amongst the histological types according to age or sex distributions. The crude survival to 4 years differed significantly for the histological types. For the entire series and for each cellular type, the nodular patterns were superior to the diffuse, although, in the lymphocytic well differentiated types, pattern made no real difference to survival.

In terms of their prognostic implications, the histological types fell into two broad groups. The nodular and diffuse lymphocytic, well differentiated and intermediately differentiated, and the nodular, mixed cell types were associated with a favourable outlook while all of the other types forecast a distinctly unfavourable prognosis.

The clinical stages were well represented in each of the histological type groups but the favourable ones were commoner in the earlier stages and the unfavourable in the more advanced.

In the 146 cases presenting in extranodal sites, a significantly higher proportion of diffuse patterns was identified and, of these, the majority were lymphocytic, poorly differentiated or " histiocytic ". The crude survival to 3 years of the former were somewhat better than the latter although the differences were not statistically significant. In most instances, the disease had extended to the regional nodes and, consequently, the survival of this group fell below that of the total series although, when the disease was confined to the primary site the survival was better. A very few cases with advanced disease and unfavourable histology, arising in the colon and the nasopharynx, survived 3 years. The gastrointestinal lesions did worse than the other extranodal sites even when clinical stage was considered. Malignant lymphoma arising in extranodal sites differs from nodal presentations in the histopathology in a direction consistent with its different clinical features.

It is concluded that the Rappaport classification of non-Hodgkin's malignant lymphoma effectively divides this group of tumours into distinct histological types between which the differences are statistically significant in terms of numerical distribution, crude survival and therefore to prognosis.

THE HISTOLOGY of 460 cases of malignant lymphoma, exclusive of Hodgkin's disease, that had been diagnosed, treated and followed at the Princess Margaret Hospital, was reviewed to evaluate Rappaport's classification (Rappaport, 1956) as a histopathological index of prognosis. The cases were taken from over 700 patients registered at the hospital in the years 1962–64, and 1967–69 inclusive. With Dr M. V. Peters (1974) and Dr. D. E. Bergsagel (1974), who reviewed the therapeutic aspects, it was agreed to exclude the patients who were under 17 years of age, those not managed entirely at the hospital, cases of chronic lymphocytic leukaemia and cases on which the slides were not available for review. The 1962–64 group comprised 185 patients and the 1967–69 included 275. The 2 groups were considered statistically similar for purposes of the histopathological analysis and were taken as one.

NUMERICAL DISTRIBUTION

In the Rappaport classification, 3 parameters—the pattern of the tumour, the cellular type and the degree of differentiation—are applied to the determination of the histological type. Individually and in combination, these dimensions contribute to the precision that the classification offers to diagnostic accuracy and prognostic value. Consequently, the numerical incidence in this series was set out in terms of both the individual and the combined parameters. Dividing the cases according to pattern, it was found that 344 (74·8%) were diffuse, that 112 (24·4%) were nodular and that 4 could not be classified. The numerical distribution of the cellular types was: lymphocytic, 285 (61·9%), mixed cell, 34 (7·4%), undifferentiated, 20 (4·4%), "histiocytic", 117 (25·5%) and unclassified, 4 (0·8%).

In combining the patterns and the cell types in the classification of the cases, the numerical distribution and the percentage that each contributed to the entire series were as set out in Table I. This shows that the predominant types were the diffuse, lymphocytic (45%), the diffuse "histiocytic" (23%) and the nodular lymphocytic (17%). The proportional contribution of the cellular types to the 2 patterns showed further differences between their distributions. The lymphocytic types constituted 70·5% of the nodular tumours and 59·8% of the diffuse. ($\chi^2 = 4{\cdot}1$, $P = 0{\cdot}04$.) The mixed cell types made up 20% of the nodular tumours but only 3% of the diffuse—a much higher proportion of the mixed cell tumours were nodular. The "histiocytic" types accounted for 31% of the diffuse and only 9% of the nodular tumours. ($\chi^2 = 21{\cdot}8, P < 0{\cdot}01$.)

When the third parameter, differentiation, is brought to bear, the influence on the lymphocytic tumours of their subdivision into well differentiated, intermediately differentiated and poorly differentiated groups comes into focus. In Table II, the numerical distribution of

TABLE I.—*Numerical Incidence by Histological Type*

Cell type	Pattern: Diffuse	Pattern: Nodular
Lymphocytic	206 (45%)	79 (17%)
Mixed (lympho-histiocytic)	11 (2%)	23 (5%)
Undifferentiated	20 (4%)	—
"Histiocytic"	107 (23%)	10 (2%)
	344	112
Unclassified	4 (0·8)	—
	460	

TABLE II.—*Numerical Incidence by Histological Type*

	Diffuse No.	Diffuse %	Nodular No.	Nodular %
Lymphocytic				
Well differentiated	29	6·3	35	7·6
Intermediate	15	3·3	4	0·8
Poorly differentiated	162	35·2	40	8·7
Mixed (lympho-histiocytic)	11	2·4	23	5·0
Undifferentiated				
Non-Burkitt	19	4·1	—	—
Burkitt	1	0·2	—	—
"Histiocytic"	107	23·3	10	2·2
Total	344		112	

the histological types, is set out with the percentage that each contributes to the entire series. Here, applying the 3 parameters in the classification, the influence of all 3 comes into play. Of the well-differentiated lymphocytic types, 29 were diffuse and 35 were nodular, but the former accounted for only 8·4% of the diffuse while the latter contributed 31·3% to the nodular group. For the poorly differentiated lymphocytic tumours, the reverse was true in that they formed 47% of the diffuse and 36% of the nodular tumours. The "histiocytic" tumours were not analysed for differentiation.

The numerical distribution of the histological types by 5-year age intervals showed no real differences amongst them, nor did their median ages differ significantly from the median age of 58 for the entire series.

Sex differences between the histological types were not significant. Of all the cases, 244 (53·6%) were men. The diffuse lesions showed a slight male sex predominance, but the women made up 56% of the nodular cases.

TABLE III.—*Histology by Stage*

Histology	Stage I	II	III	IV	Total
Diffuse					
Lymphocytic W.D.	11	6	7	5	29
Lymphocytic I.D.	2	6	6	1	15
Lymphocytic P.D.	31	41	48	42	162
M.C. (L/H)	2	5	1	3	11
Undifferentiated	3	6	4	6	19
(Non-Burkitt)	—	—	—	—	—
Burkitt type	—	—	1	—	1
"Histiocytic"	16	33	23	35	107
Unclassified	1	—	1	2	4
Nodular					
Lymphocytic W.D.	9	10	14	2	35
Lymphocytic I.D.	—	2	2	—	4
Lymphocytic P.D.	9	8	13	10	40
M.C. (L/H)	5	6	10	2	23
"Histiocytic"	2	4	2	2	10
Total	91	127	132	110	460

TABLE IV.—*Numerical Distribution by Pattern and by Stage*

Stage	Histology: Diffuse	Nodular	Total*	Percentage diffuse
I	65	25	91	71·4
II	98	30	128	76·6
III	90	41	132	68·2
IV	90	17	109	82·6
Total	343	113	460	74·5

* Including the unclassified patients.

CLINICAL STAGE AND HISTOLOGICAL TYPE

The numerical distribution of the histological types by clinical stage is recorded in Table III. The stage classification employed was that described by Peters *et al.* (1974). The stages were evenly represented in the series and the only real difference identified was between the 2 patterns. The distribution of the cases by pattern and stage is shown in Table IV, with the percentage of diffuse patterns which was highest in the Stage IV cases, of which 82·6% were diffuse compared with 72% for Stages I, II and III combined. This difference is significant at the 95% level ($\chi^2 = 4{\cdot}8$). As for the individual types, the lymphocytic, well differentiated, constituted a higher proportion of the Stage I cases whereas more of the "histiocytic" and the undifferentiated types were found in the advanced stages, although the differences were not statistically significant.

SURVIVAL AND HISTOLOGICAL TYPE

In this series, the histological types were analysed by crude survival at 4 years. The first difference identified was between the patterns. Taken together, all of the nodular cases had a 67% survival, in contrast to the 33% for the diffuse types. The curves for the 2 patterns, with that of the overall survival, are illustrated in Fig. 1. The median overall survival was just under 30 months; for the nodular types it was more than 60 months; less than half the patients with diffuse disease lived 18 months after diagnosis. Furthermore, the superior survival of the nodular types over the diffuse was sustained for each cell type. This is illustrated in Fig. 2. The survival at

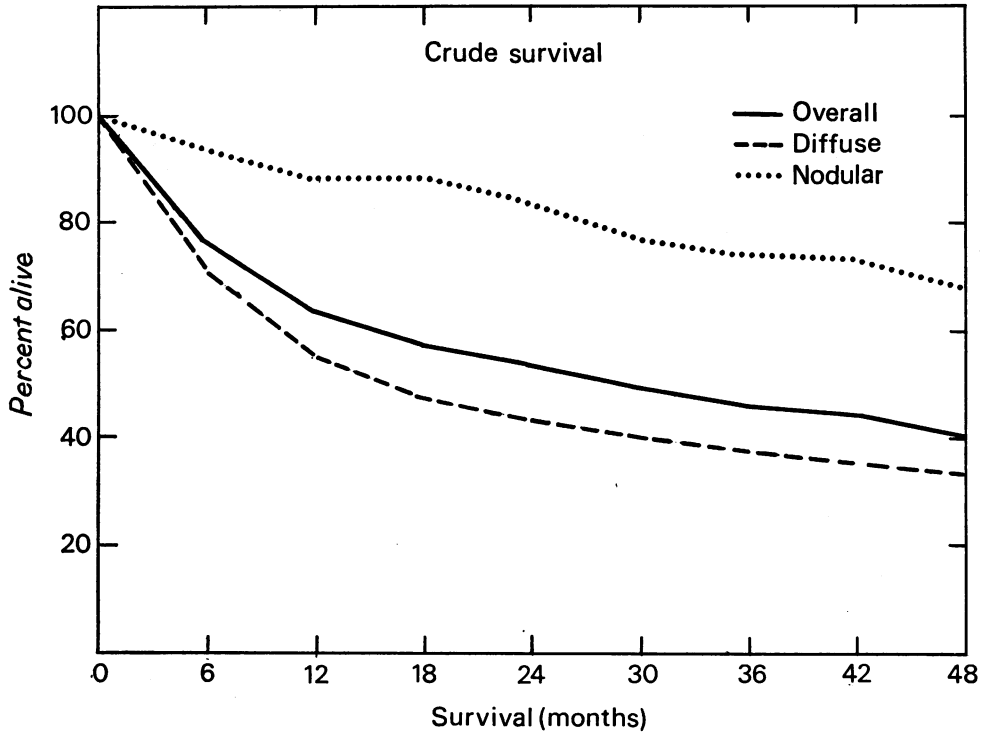

FIG. 1.—Non-Hodgkin's lymphoma: crude survival and histological pattern.

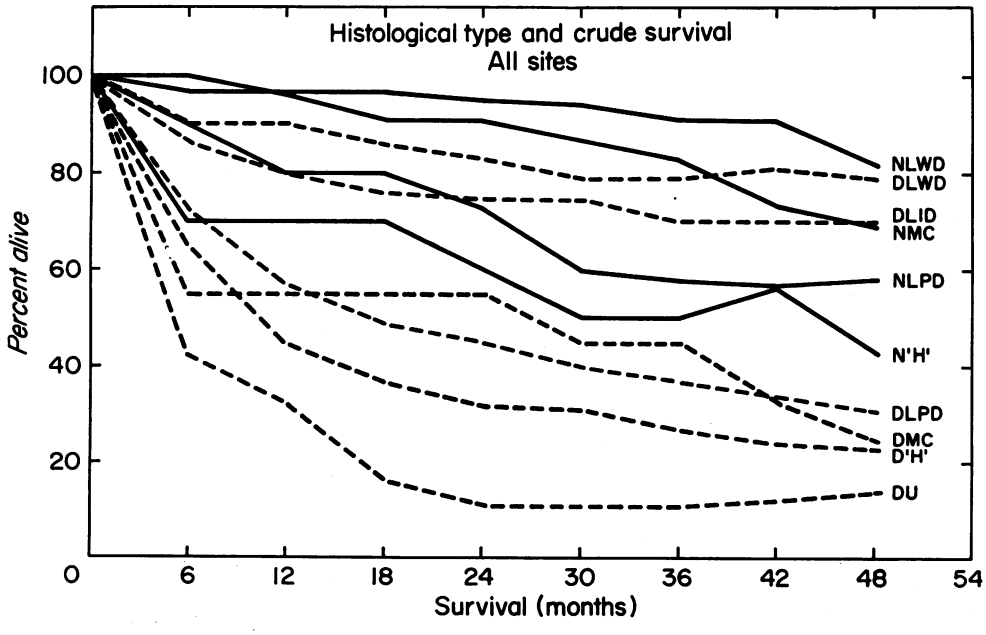

FIG. 2.—Non-Hodgkin's lymphoma: crude survival according to histological category.

TABLE V.—*Survival Rates at 1 Year, 2 Years, and 4 Years—Histological Classification*

	Interval after diagnosis					
	One year		2 years		4 years	
Histology	No.	Rate	No.	Rate	No.	Rate
Diffuse	346	54·9	346	43·1	282	32·6
L.W.D.	29	89·6	29	82·7	24	79·1
L.I.D.	15	80·0	15	66·6	13	61·5
L.P.D.	161	56·5	161	44·7	136	30·9
M.C.	11	54·5	11	54·5	8	25·0
U. non-Burkitt	19	31·6	19	10·5	14	14·3
U. Burkitt	1	*	*	*	*	*
'Histiocytic"	106	45·3	106	32·1	83	22·9
Unclassified	4	*	*	*	*	*
Nodular	113	88·5	113	83·2	77	67·5
L.W.D.	35	97·1	35	94·3	18	83·3
L.I.D.	5	*	*	*	*	*
L.P.D.	40	80·0	40	72·5	31	58·1
M.C.	23	95·6	23	91·3	16	68·7
"Histiocytic"	10	70·0	10	60·0	7	42·8
Total	459	63·2	459	52·9	359	40·1

* Not shown for fewer than 10 patients.

one, 2 and 4 years by histological classification is recorded in Table V, from which the prognostic significance of the classification is determined. Considering first the lymphocytic cell types, of the well differentiated, the survival of the nodular patterns was 83·3% and that of the diffuse 79·1%. Statistically, a significant difference could not be established for the apparent superiority of the nodular over the diffuse forms. On the other hand, for the poorly differentiated lymphocytic tumours, the survival for the nodular patterns was 58% compared with that for the diffuse of 31% and this difference is significant ($\chi^2 = 7$, $P = 0{\cdot}003$).

The degree of differentiation was an important factor in the lymphocytic cellular types. Between the well differentiated and the poorly differentiated the difference is statistically significant ($\chi^2 = 18{\cdot}0$, $P =$ less than 0·001). The difference between the intermediately differentiated and the poorly differentiated lymphocytic tumours was also significant ($\chi^2 = 37$, $P = 0{\cdot}04$); but no real difference could be demonstrated between the well differentiated and the intermediately differentiated groups. However, the curve for the latter (Fig. 2) falling midway between that for the well differentiated and the poorly differentiated, suggests that the intermediates may be a separate entity. The conformity of its curve, after 30 months, to that of the well differentiated, points to a closer resemblance to the latter.

Patients with "histiocytic" and undifferentiated cell types showed a poor survival. Among the histiocytic tumours, the 22% survival for the diffuse was distinctly worse than that for the nodular forms but the small numbers of the latter were insufficient to establish significance for the differences in this group.

The survival curves for the lymphocytic, poorly differentiated, the "histiocytic" and the undifferentiated tumours (Fig. 2) emphasized the descending order of survival although the differences were not found statistically significant.

For the mixed cell types, the 68·7% survival for the nodular patterns was significantly different to the 25% survival for the diffuse types. Again in Fig. 2, it is clear that the nodular mixed cell tumours rank among the good survivors, with the lymphocytic, well differentiated and the intermediately differentiated tumours. On the other hand, the diffuse mixed cell tumours fall in with the poor survivors and, as is seen in the graph (Fig. 2), approximate the survival for the diffuse lymphocytic, poorly differentiated tumours.

Comment

In the application of the Rappaport classification to these cases, statistically significant differences were found between the histological types according to their numerical incidence and to their crude survivals to 4 years. The differences obtained for the patterns of growth, for the cell types and the degrees of differentiation in the lymphocytic group—for

each parameter separately and as they are combined in the classification to designate the histological types. Of greatest significance was the pattern. The cellular types, dominated numerically by the lymphocytics, showed distinct predilections to the 2 different growth patterns. It was this modulating influence of the parameters on each other that provided the identity of the distinctive types in the classification.

As a group, the lymphocytics, most of which were diffuse, actually contributed a higher proportion of the nodular cases than they did to the diffuse. This was clearly the case for the well differentiated types, whereas the poorly differentiated were predominantly diffuse both numerically and proportionately. The intermediate group, more of which were diffuse, tended to be better represented in the nodular patterns. The mixed cell lesions were nodular in large measure and constituted a much higher proportion to the nodular tumours than they did to the diffuse. The " histiocytic " group was almost entirely diffuse.

No difference in the numerical distribution of the histological types was found according to the age or to the sex of the patient. Amongst the 4 clinical stages, there was some tendency for the well differentiated lymphocytic tumours, both nodular and diffuse, and the nodular mixed cell type to appear in Stages I and II while the " histiocytic " and undifferentiated were commoner in Stages III and IV.

The crude survival to 4 years among the histological types differed to a significant degree. For each cell type in which pattern was a factor, the nodular was clearly better than the diffuse excepting the lymphocytic, well differentiated tumours where it seemed to make no real difference. From the standpoint of survival, the separate histological types in the classification tended to divide themselves into prognostically favourable tumours or prognostically unfavourable tumours. The former were the diffuse and nodular lymphocytic, well differentiated and intermediately differentiated and the nodular, mixed cell types.

PRESENTATION IN EXTRANODAL SITES

In this series, the malignant lymphoma first developed in an extranodal site in 146 of the 460 cases, or 37% of the series. The histological types, the clinical stages and the crude survivals to 4 years of tumours arising in extranodal sites were compared with those presenting in lymph nodes and some differences were found. Commoner in extranodal sites was the diffuse pattern and, as shown in Table VI, 87·6% of these were diffuse compared with 68·4% in the nodal presentations. This difference is significant at the 99% confidence level ($\chi^2 = 18{\cdot}7$, $P = 0{\cdot}01$).

TABLE VI.—*Summary of Presentation (Nodal* vs. *Extranodal) by Diffuse or Nodular Classification*

Presentation	Histological classification		Total	Percentage diffuse
	Diffuse	Nodular		
Nodal	215	96	314	68·4
Extranodal	128	17	146	87·6
Total	343	113	460	74·6

The numerical distribution of the cellular types is compared in Table VII, which also shows the percentage of each cell type arising in an extranodal site. Of the 146 extranodal presentations, 74 were lymphocytic, poorly differentiated, 40 were " histiocytic " and the other types were represented by relatively small numbers. Of the diffuse lesions, 54·3% were lymphocytic, poorly differentiated, 27% were " histiocytic ", and 3·9% were of the mixed cell type. On the other hand, for the nodular patterns, 23·5% were lymphocytic, poorly differentiated, 30% were " histiocytic " and 23·5% mixed cell. Thus, in extranodal sites,

TABLE VII—*Presentation* (*Nodal* vs. *Extranodal*) *by Histological Classification*

Histology	Presentation: Nodal	Presentation: Extra-nodal	Total	Percentage extra-nodal
Diffuse	215	128	343	37·3
L.W.D.	23	6	29	20·7
L.I.D.	12	3	15	20·0
L.P.D.	92	70	162	43·2
M.C.	6	5	11	45·5
Undifferentiated (Non-Burkitt)	11	8	19	42·1
Burkitt	—	—	—	—
" Histiocytic "	—	1	1	0
Nodular	71	35	106	33·0
L.W.D.	96	17	113	15·0
L.I.D.	32	3	35	8·6
L.P.D.	4	1	5	0
M.C.	36	4	40	10·0
" Histiocytic "	19	4	23	17·4
Unclassified	5	5	10	50·0
Total	3	1	4	0
	314	146	460	31·7

the lymphocytic, poorly differentiated is the prevalent type and is usually diffuse. No relative difference between the nodular and diffuse patterns was found for the " histiocytic " types but the nodular pattern was somewhat commoner in the lymphocytic, well differentiated and the mixed cell types.

The numerical distribution by clinical stage for the diffuse and the nodular patterns is compared for nodal and extranodal presentations in Table VIII. In extranodal sites, for all stages, the percentage of diffuse patterns is higher than in the nodal sites and in the latter only in Stage IV does this percentage approach that for the extranodal sites.

SPECIFIC EXTRANODAL SITES

Although the disease arose in many different extranodal sites, the histological types could only be compared for those most often affected. To this end, the extranodal presentations were divided into 4 groups—the upper respiratory and oral, the gastrointestinal, the bones and the other sites. These were considered separately.

Upper respiratory tract

Forth-seven cases arose in the upper respiratory tract and oral cavity. Of these 20 appeared in the tonsils, 16 in the nasopharynx, 7 in the nasal accessory sinuses and 4 in the mouth, including the hard palate, the tongue and the buccal mucosa. In Table IX, the distribution of the histological types is recorded. Of these, 87·2% were diffuse lesions. The difference between the incidence of the diffuse and the nodular patterns is significant ($\chi^2 = 4{\cdot}4$, $P = 0{\cdot}03$). The lymphocytic, poorly differentiated and the " histiocytic " were the predominant cellular types. The diffuse lymphocytic, well differentiated was identified in 3 cases, 2 of them in the nasopharynx. The undifferentiated, non-Burkitt type accounted for 3 cases in the tonsils.

TABLE VIII.—*Presentation* (*Nodal* vs. *Extranodal*) *by Stage and by Diffuse or Nodular Classification*

Presentation	Stage	Histological classification: Diffuse	Histological classification: Nodular	Total	Percentage diffuse
Nodal	I	31	23	54	57·4
	II	64	25	89	71·9
	III	55	36	92	59·8
	IV	65	12	79	82·3
Total		215	96	314	68·4
Extranodal	I	34	2	37	91·9
	II	34	5	39	87·2
	III	35	5	40	87·5
	IV	25	5	30	83·3
Total		128	17	146	87·6

TABLE IX.—*Histological Classification of Patients Presenting with Specified Extranodal Sites*

Histology	Extranodal site				
	Nasopharynx	Tonsil	Sinus	Other*	
Diffuse	14	20	5	2	41 (87·2%)
L.W.D.	2	0	0	1	3
L.I.D.	0	0	0	0	0
L.P.D.	9	10	4	1	24
M.C.	0	0	0	0	0
U. N/B	0	3	0	0	3
" Histiocytic "	3	7	1	0	11
Nodular	2	0	2	2	6 (12·8%)
L.W.D.	0	0	0	0	0
L.I.D.	0	0	0	1	1
L.P.D.	2	0	0	0	2
M.C.	0	0	1	1	2
" Histiocytic "	0	0	1	0	1
Total	16	20	7	4	47

* Hard palate, tongue, buccal mucosa.

The crude survival rates at one and 3 years for each site and for all the histological types are shown in Table X.

TABLE X.—*Survival at 1 Year and at 3 Years for Patients Presenting with Specified Extranodal Sites*

Extranodal site	1 year		3 years	
	Alive/at risk	Rate	Alive/at risk	Rate
Nasopharynx	13/16	81	9/16	56
Tonsil	11/20	55	5/20	25
Sinus	6/7	86	3/7	43
Other sites	4/4	0	4/4	0
Total	34/47	72	21/47	45

Only 25% of the patients survived when the lymphoma presented in the tonsil, whereas presentation in the nasal accessory sinuses and the nasopharynx was associated with a somewhat better survival.

The relation between survival and clinical stage at one and 3 years for the different anatomical sites is recorded in Table XI. Although the tonsillar group is the largest, only 15% of the tumours were Stage I and 70% were Stage II and its survival of 14% was the poorest of the group. Lesions arising in the nasopharynx did somewhat better with 30% being in Stage I and 56% in Stage II. In the sinuses, Stage I disease was found in 57% and this stage constituted 50% of the lesions involving the other sites in this group. The crude survival rates by clinical stage were compared for the diffuse lymphocytic, poorly differentiated and for the diffuse " histiocytic " tumours. Where the numbers of cases were sufficient to evaluate, it appeared that in Stages I and II, the lymphocytic tumours had a somewhat better survival than the " histiocytic " but that in Stages III and IV the survival of both these types was poor. This is recorded in Table XII.

In this group of extranodal presentations, the outlook for tumours arising in the tonsils was poor because the disease had usually extended beyond the primary site even though, in most cases, this was only to the regional nodes. However, when the disease was confined to the tonsil, the patients did as well as those in whom it had arisen in the nasopharynx and yet, as a group, the nasopharyngeal cases did better than the tonsillar presentations due mainly to the better survival of the Stage II cases. In all of these sites, the diffuse lymphocytic

TABLE XI.—*Survival at 1 Year and at 3 Years for Patients Presenting with Specified Extranodal Sites by Stage of Disease at Diagnosis*

Extranodal site	Stage	1 year		3 years	
		Alive/at risk	Rate	Alive/at risk	Rate
Nasopharynx	I	5/6	83	4/6	66
	II	8/9	89	5/9	56
	III and IV	0/1	0	0/1	0
Tonsil	I	3/3	0	3/3	0
	II	8/14	57	2/14	14
	III and IV	0/3	0	0/3	0
Sinus	I	4/4	0	2/4	0
	II	1/1	0	1/1	0
	III and IV	1/2	0	0/2	0
Other sites	I	2/2	0	2/2	0
	II	1/1	0	1/1	0
	III and IV	1/1	0	1/1	0
Total	I	14/15	93	11/15	73
	II	18/25	72	9/25	36
	III and IV	2/7	28	1/7	14
Total		34/47	72	21/47	45

TABLE XII.—*Survival Rates by Stage for Patients Classified as D.L.P.D. or D"H"*

Histological classification	Stage	No. at risk	Alive at 1 year		Alive at 3 years	
			No.	Rate	No.	Rate
		" Upper respiratory "				
D.L.P.D.	I	8	8	100	6	75
	II	6	4	67	3	50
	III	4	3	0	1	0
	IV	6	2	33	0	
	Total	24	17	71	10	41
D" H "	I	2	1	0	1	0
	II	5	3	60	2	40
	III	3	2	0	0	0
	IV	1	0	0	0	0
	Total	11	6	54	3	27

tumours did better than the " histiocytic ".

Gastrointestinal lesions

Of the 56 cases that presented in the gastrointestinal system, 28 arose in the stomach, 18 in the small intestine and 10 in the large intestine. The numerical distribution of the histological types is set out in Table XIII. In these sites, over 90% of the lesions were diffuse as were all of those arising in the large intestine. This was true for all of the lymphocytic poorly differentiated, the " histiocytic " and together these accounted for 42 of the 56 cases. In the large intestine, the " histiocytic " type was relatively commoner than in the other 2 sites. A single case of undifferentiated non-Burkitt lymphoma was found in each of the sites and one case of undifferentiated Burkitt type was identified in the small intestine. None the less, the proportion of cases with diffuse disease was somewhat lower in the small intestine.

The crude survival at one and 3 years

TABLE XIII.—*Histological Classification of Patients Presenting with Extranodal Sites in the G.I. System*

	Extranodal site			
Histology	Stomach	Small intestine	Large intestine	Total
Diffuse	26	15	10	51
L.W.D.	2	1	0	3
L.I.D.	1	1	0	2
L.P.D.	14	8	4	26
M.C.	2	1	1	4
U. non-Burkitt	1	1	1	3
U. Burkitt	0	1	0	1
"H"	6	2	4	12
Nodular	2	3	0	5
L.W.D.	2	0	0	2
L.I.D.	0	0	0	0
L.P.D.	0	0	0	0
M.C.	0	2	0	2
"H"	0	1	0	1
Total	28	18	10	56
Percentage diffuse	92·8	83·3	100·0	91·1

TABLE XIV.—*Survival at 1 and at 3 Years, Patients Presenting with Extranodal Sites in the G.I. System*

Extranodal site	No. at risk	Alive at 1 year		Alive at 3 years	
		No.	Rate	No.	Rate
Stomach	28	14	50	11	39
Small intestine	18	7	38	6	33
Large intestine	10	5	50	3	30
All G.I. system	56	26	46	20	36

for each of the gastrointestinal sites is recorded in Table XIV. The prognosis of all of the sites is poor, with the stomach somewhat better than the intestine. For each site, the crude survival at one and 3 years by clinical stage is recorded in Table XV. The survival was best for the 10 lesions arising in the large intestine; 5 of these were confined to the intestinal wall and in 4 more it had spread only to the regional nodes. Nevertheless, only the Stage I lesions survived 3 years. In the small intestine, the survival was the poorest but, 14 of 18 cases were Stage II and 3 were in Stages III and IV. The gastric lesions, numerically the largest group, had the best survival although 19 of the 28 cases were in Stage II. In comparing the survivals of the gastric versus the small intestinal lesions, the poorer outlook for the latter is emphasized by the 28% survival at one year in Stage II lesions compared with 58% for the gastric lesions.

The diffuse, lymphocytic, poorly differentiated and the diffuse, "histiocytic" types arising in these sites were compared by clinical stage as in Table XVI. The survivals for the two were essentially equal and in the lymphocytic group there appeared to be a direct relationship between clinical stage and survival. The

TABLE XV.—*Survival at 1 and at 3 Years by Stage for Patients Presenting with Extranodal Sites in the G.I. System*

Extranodal site	Stage	1 year		3 years	
		Alive/at risk	Rate	Alive/at risk	Rate
Stomach	I	1/2	0	1/2	0
	II	11/19	58	8/19	42
	III and IV	2/7	28	2/7	28
	Total	14/28	50	11/28	39
Small intestine	I	1/1	0	1/1	0
	II	4/14	28	4/14	28
	III and IV	2/3	0	1/3	0
	Total	7/18	38	6/18	33
Large intestine	I	4/5	80	3/5	60
	II	1/4	0	0/4	0
	III and IV	0/1	0	0/1	0
	Total	5/10	50	3/10	30

TABLE XVI.—*Survival Rates by Stage for Patients Classified as D.L.P.D. or D "H"*

Histological classification	Stage	No. at risk	Alive at 1 year		Alive at 3 years	
			No.	Rate	No.	Rate
		G.I. System				
D.L.P.D.	I	3	1	0	1	0
	II	7	5	71	4	56
	III	14	2	14	1	7
	IV	6	3	50	2	33
	Total	30	11	37	8	27
D" H "	I	2	2	0	1	0
	II	3	2	0	2	0
	III	3	1	0	0	0
	IV	4	0	0	0	0
	Total	12	5	42	3	25

TABLE XVII.—*Survival at 1 Year and at 3 Years, Patients Presenting with Certain Extranodal Sites by Stage*

Extranodal site	Stage	1 year Alive/at risk	1 year Rate	3 years Alive/at risk	3 years Rate
Bone	I	7/9	77	4/9	44
	II	1/2	0	0/2	0
	III	1/1	0	0/1	0
	IV	0/2	0	0/2	0
	Total	9/14	64	4/14	28

numbers of cases were too small to compare the 2 cell types by stage as between the separate sites.

Bone

In this series, 13 cases arose in the osseous system and all but one were of the diffuse pattern. Seven were of the "histiocytic" type and 6 were lymphocytic, poorly differentiated. The crude survival of these cases at one and 3 years by stage, as recorded in Table XVII, shows that at 3 years the only survivors were 4 of 9 cases of Stage I disease. As in Table XVIII, the survival rates by stage for the cases classified as diffuse lymphocytic, poorly differentiated and diffuse "histiocytic" were compared. For both, the majority were in Stage I and of these 2 of each type survived 3 years. One case of each was in Stage IV. None of the "histiocytic" cases beyond Stage I survived for more than one year but 2 of the lymphocytic cases did. These results could only suggest that patients with malignant lymphoma arising in

TABLE XVIII.—*Survival Rates by Stage for Patients with D.L.P.D. or D "H" and Bone Involvement*

Histological classification	Stage	No. at risk	Alive at 1 year		Alive at 3 years	
			No.	Rate	No.	Rate
		Bone				
D.L.P.D.	I	3	3	0	2	0
	II	1	1	0	0	0
	III	0	0	0	0	0
	IV	1	1	0	0	0
	Total	5	5	100	2	40
D" H "	I	4	3	0	2	0
	II	2	0	0	0	0
	III	0	0	0	0	0
	IV	1	0	0	0	0
	Total	7	3	42	2	28

bone but extending beyond it do poorly, while those in whom the lesion is confined to bone do well: those with lymphocytic disease have a somewhat better outlook than those with " histiocytic " disease.

Other extranodal sites

The remaining 24 cases had presented in other extranodal sites. These included the thyroid, apparently involved primarily in 7 patients, the spinal extradural tissues in 4, the breast and the testis in 3 each, the skin and the lung in 2 each and finally in a single instance, the kidney, the ovary and the ocular orbit.

Twenty-one (87%) of the lesions had a diffuse pattern. Of these, 10 were lymphocytic, poorly differentiated, 8 were " histiocytic " to which were added one each for the mixed cellular, the lymphocytic, well differentiated and the lymphocytic, intermediately differentiated types. The nodular lesions included a single case for each of the lymphocytic, poorly differentiated, the mixed cellular and the lymphocytic, well differentiated types. Involved predominantly by the diffuse, lymphocytic, poorly differentiated and the diffuse " histiocytic " types were the thyroid, the testis, the spinal extradural tissues and the skin. Both the cutaneous lesions and the renal tumour were diffuse, " histiocytic ". One mammary lesion was diffuse, mixed cell and 2 were lymphocytic well differentiated. One of the pulmonary tumours was diffuse " histiocytic " and one was diffuse, lymphocytic, well differentiated. The ovarian tumour was diffuse lymphocytic, poorly differentiated. The nodular mixed cell type was found in one thyroid case. Although the less well differentiated types predominated, 16 of them survived one year and 12 (50%) were alive after 3 years.

When the miscellaneous extranodal sites were involved in instances of widespread disease, the cases were taken as nodal presentations.

Comment on the extranodal sites

The crude survival rates for the extranodal site group were analysed at one and 3 years as these were considered the significant time intervals to the evaluation of prognosis. This is borne out by the analysis of the 10-year survivals of the 185 cases in the 1962–64 group reported by Peters *et al.* (1974). These showed that the differences in survival developed during the first 3 years, after which the rate of deterioration in the survival was lessened as the curves flattened.

Taken together, the cases that presented in the upper respiratory tract, including Waldeyer's ring and the oral cavity, showed a crude survival to 3 years equivalent to that of the other extranodal sites, with the nasopharyngeal doing somewhat better. For this group, the initial extent of the disease was a significant factor to prognosis and the survival of Stage I cases was considerably above the average for the series. In Stage II cases, the nasopharyngeal cases did relatively well in comparison with the tonsillar cases. The survival of the diffuse, lymphocytic, poorly differentiated histiological type was somewhat better than the diffuse " histiocytic " cases, even though the latter showed a higher concentration of Stage II cases while the lymphocytics were well distributed amongst the stages.

The tumours that arose in the gastrointestinal tract showed a poorer survival than that for the other extranodal sites. Of these, 90% were of the diffuse pattern and 75% were either lymphocytic, poorly differentiated, " histiocytic " or undifferentiated. A higher proportion of them extended beyond the primary site but their lower survival was sustained even when stage was taken into consideration. The tumours arising in the stomach had a better outlook than those arising in the intestine. The large intestine had the highest proportion of Stage I lesions, and in this stage, a crude survival rate to 3 years of 63% obtained for all the gastro-

intestinal presentations. The better than expected survival of the " histiocytic " tumours of these organs may have been due to chance variation.

The crude survival of the cases arising in bone was only 28% and only when the lesion was confined to bone did any of the patients survive 3 years. All of the tumours were diffuse and either of the lymphocytic poorly differentiated or " histiocytic " types and no real difference in survival could be demonstrated between them.

Of the tumours arising in the miscellaneous extranodal sites, 87% were of the diffuse pattern and 83% were of the unfavourable histological type. Nevertheless, 50% of them were alive at 3 years, the best survival among the extranodal sites, although this probably reflects the preponderance of early stage lesions.

Considering the extranodal site presentations as a group, they tended to be of the unfavourable histological types and the majority were at least Stage II. When the disease was confined to the primary site, the prognosis tended to be better than that for the entire series. However, once the disease had spread, the survival declined usually to a level below that of the entire series. Rarely, however, disease arising in an extranodal site and extending beyond it, survived 3 years. The proportion of lesions with a diffuse pattern was slightly higher for the gastrointestinal tract. The crude survival of the diffuse, lymphocytic, poorly differentiated histological types was somewhat better than that for the diffuse, " histiocytic " although the difference between them was not significant. In general, tumours arising in the gastrointestinal tract did worse than the other sites, but they include a higher proportion of tumours that extended beyond the viscus even though their poor survival obtained even when stage was taken into consideration.

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